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# REIMBURSEMENT OF CELL- BASED REGENERATIVE THERAPY IN THE UK AND FRANCE

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## Summary:

Cell- based regenerative therapies are presented as being able to cure the diseases of the XXI century, especially those coming from the degeneration of the aging human body. But their specific nature based on biological materials raises particular challenging issues on how regulation should frame biomedical innovation for society's benefit regarding public health. The European Union (EU) supports the development of cell- based regenerative therapies that are medicinal products with a specific regulation providing their wide access to the European market for European patients. However, once these medicinal products have obtained a European marketing authorisation, they are still far away from being fully accessible to European patients in all EU Member States. Whereas there is much written on the EU regulatory system for new biotechnologies, there is no systematic legal study comparing the insurance provisions in two EU countries. Focusing on the situation in the United Kingdom and France that are based on two different healthcare systems, this paper is based on a comparative methodological approach. It raises the question of regulatory reimbursement mechanisms that determine access to innovative treatments, and their consequences for social protection systems in the general context of public health. After having compared the French and English regulations of cell- based regenerative therapy regarding pricing and

reimbursement, this paper analyses how England and France are addressing two main challenges of cell-based regenerative therapy, to take into account their long-term benefit through their potential curative nature and their high up front cost, towards their adoption within the English and French healthcare systems. It concludes that England and France have different general legal frameworks that are not specific to the reimbursement of cell-based regenerative therapy although their two current and respective trends would bring more convergence between the two systems while addressing the main challenges for the reimbursement of these therapies. Nevertheless, despite their current differences neither the English nor the French national healthcare systems have yet approved the reimbursement of cell-based regenerative therapies. The paper highlights where both systems could be learning from each other experiences to favour the adoption of cell-based regenerative therapies through the adaptation of their reimbursement methodologies. It also emphasizes the gap between market access and patients' access and, it calls for research and discussions through reflexive agencies such as Regenerative Medicine Expert Group in the UK.

**Keywords:** Regenerative therapy, pricing, reimbursement, access, England, France

**Main Text:**

## I- INTRODUCTION

Cell-based regenerative therapies are presented as being able to cure the diseases of the XXI century, especially those coming from the degeneration of the aging human body. Regenerative therapy should be considered as part of 'regenerative medicine'. Although 'regenerative medicine' has been widely defined within the UK Strategy on Regenerative Medicine,<sup>1</sup> it is not a legal concept that is strictly defined and delimited at the European Union level. For the purposes of this paper, I will focus on cell therapy medicinal products and tissue

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<sup>1</sup> "For the purposes of this strategy, regenerative medicine has been defined as an interdisciplinary approach spanning tissue engineering, developmental and stem cell biology, gene therapy, cellular therapeutics, biomaterials (scaffolds and matrices), nanoscience, bioengineering and chemical biology that seeks to repair or replace damaged or diseased human cells or tissues to restore normal function". UK Councils (BBSRC, EPSRC, ESRC, MRC) and TSB, A Strategy for UK Regenerative Medicine, March 2012, p2.

engineered products under the term ‘cell- based regenerative therapies’, that are part of regenerative therapy, i. e. the use of human cells and tissues that are transformed into medicinal products for therapeutic purposes. Although the exceptional nature of regenerative medicine can be discussed,<sup>2</sup> from a legal point of view cell- based regenerative therapy has been specifically regulated both for economic and public health objectives. Cell- based regenerative therapy has been foreseen as a factor of economic growth. This market is perceived lucrative as it could foster the competitiveness of European biotechnology companies and be a key to national prosperity. In addition cell- based regenerative therapy would offer new therapeutic perspectives in curing causes more than treating symptoms of the diseases only; its claimed value being long term benefits from a single or very limited number of treatment. A wide range of diseases could be covered, notably those for which no or insufficient treatments exists, such as neurological, cardiovascular, orthopaedic diseases or cancers. Public health regulation is consequently a combination of a will to provide a wide accessibility of medicine to patients while minimising the risks of these novel and complex therapies that rely on technical specificities of processes and products. The regulation currently covers the entire life- cycle of cell-based regenerative therapies from tissues and cells procurement to the pharmacovigilance of the authorised medicinal products, going through manufacturing, clinical trials, marketing authorisation, pricing, reimbursement, information and advertisement and even patentability. However, such regulation is quite complicated especially as it is based on different laws. At the European Union level, a specific regulation on Advanced Therapy Medicinal Products has been adopted in 2007 with the main objectives of providing the free movement of cell- based regenerative therapies within the European Union market while ensuring a high level of protection of public health.<sup>3</sup> But such

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<sup>2</sup> J Gardner, A Faulkner, A Mahalatchimy, A Webster, ‘Are there specific translational challenges in regenerative medicine? Lessons from other fields’ (2015) 10(7) Regenerative Medicine, 885- 895.

<sup>3</sup> Regulation (EC) n°1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) n°726/2004 [2007] OJ L324/121..

specific European regulation to promote cell- based regenerative therapy to access the market does not imply *ipso facto* the patients' access to the authorised medicinal products. Indeed, the concrete adoption of these products within the health care systems depends on national decisions and regulations in accordance with the EU treaties. One can consider that an authorised medicinal product is fully accessible to patients when it is both effectively commercialised in a country and when its cost is entirely covered by the national health insurance system. The two countries that will be compared are the UK that has a particular national strategy on regenerative medicine, and France that does not. The UK national strategy notably gives rise to the setting- up of a Regenerative Medicine Expert Group (RMEG) that provided an extensive report on this topic, including on the adoption of regenerative medicine in the clinic.<sup>4</sup> Even though both countries are Member States of the European Union, which means that they are legally embedded within the EU regulatory promotion of cell- based regenerative therapy to access the market, the UK has a Beveridge model while France has a Bismarck model.<sup>5</sup> In the UK, the system is mainly public and centralised. The State power ensures the financing of the system through taxes and not through social contributions as in France. Except in specific cases, the patients do not directly pay but have to be cared by public health care providers (the National Health Service- NHS) or by providers having an agreement with the NHS to benefit from free health care. In this paper, I will focus on England because reimbursement of drugs relies on different national authorities in Scotland, Wales and Northern Ireland. In France, the system is based on mandatory health insurance regimes funded by the collection of social contributions. The (total or partial) reimbursement of health care is provided whoever the health care provider is, being either public or private. While it can be considered that there is an increasing

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<sup>4</sup> Regenerative Medicine Expert Group, Building on our own potential: a UK pathway for regenerative medicine, Her Majesty's Stationery Office, 2015.

<sup>5</sup> For a recent and general International review, see notably: R Kulesher, E Forrestal, 'International models of health systems financing' (2014) 3(4) Journal of Hospital Administration, 127- 139.

convergence between these two models that can be complementary,<sup>6</sup> the aim of this paper is not to discuss their main differences as such as they have already been widely commented on, but rather to consider the different pathways that are relevant to cell- based regenerative medicine in both of them and that are not linked to the choice of different healthcare system models: On the basis of a comparative approach, how do English and French laws allow the adoption of centrally authorised (European level) cell- based regenerative therapies within their national healthcare systems? As a matter of fact, among the four cell- based regenerative therapies that have obtained a centralised marketing authorisation (ChondroCelect, MACI, Provenge, Holoclar),<sup>7</sup> granted by the European Commission after positive opinion of the European Medicines Agency (EMA) involving the Committee for Advanced Therapies (CAT), none of them is covered by the UK or French national health insurance systems yet. Particularly, even though ChondroCelect has been the first cell- based regenerative therapy that obtained a European marketing authorisation in 2009, renewed in 2014, it is not presently reimbursed in the UK or France by public national insurances. Hence, one can wonder whether the current regulatory frameworks are adapted to the particular challenges raised by the reimbursement of regenerative medicine: mainly a balance has to be found between their high up front cost<sup>8</sup> and their potential impact on public health if they attain their curing potential in a context of uncertainty with evidences and limited health resources.

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<sup>6</sup> J Kutzin, Coordinator at WHO, Bismarck vs. Beveridge: is there increasing convergence between health financing systems, 1<sup>st</sup> annual meeting of SBO network on health expenditure, 21- 22 November 2011, Paris, OECD.

<sup>7</sup> Although Glybera is another ATMP that has obtained a centralized marketing authorization, it is excluded from the scope of this paper as it was classified as a gene therapy medicinal product by the Committee for Advanced Therapies at the EMA.

<sup>8</sup> It exists a huge variety of prices according to the drug and the country considered but the cost of regenerative medicine is usually perceived as high (50, 000 to 100, 000 american dollards) or very high (500, 000 to 1 million american dollards). To see notably: DW Freeman, Dendreon's \$93,000 prostate cancer drug: is Provenge worth it?, CBS News, 31 March 2011: <<http://www.cbsnews.com/news/dendreons-93000-prostate-cancer-drug-is-provenge-worth-it/>>; B Hirschler, Analysis: Entering the age of the \$1 million medicine, Reuters, 3 January 2013:<<http://www.reuters.com/article/2013/01/03/us-rarediseases-idUSBRE9020C120130103>>; C. Mason, DA Brindley, EJ Culme-Seymour, NL Davie, 'Cell therapy industry: billion dollar global business with unlimited potential' (2011) 6(3) Regenerative Medicine, 265- 272.

After having compared the French and English regulations of cell- based regenerative therapy regarding pricing and reimbursement (II), I will analyse how England and France are addressing the two main reimbursement challenges towards the adoption of cell- based regenerative therapy within the English and French healthcare systems (III).

## II- PRICING AND REIMBURSEMENT OF CELL- BASED REGENERATIVE THERAPY IN ENGLAND AND FRANCE

We will first consider the main principles for reimbursement and pricing in both countries (A) before focusing on the specific regulatory pathways that can be used for cell-based regenerative therapies (B). But, first of all it should be highlighted that the European directive 89/105/CEE relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance system notably requires Member States to adopt their decision on reimbursement and to communicate it to the applicant within 180 days of an application submitted after the granting of the marketing authorisation.<sup>9</sup>

### *A. Main principles for reimbursement and pricing*

Both in England and France, separate rules for reimbursement (1) and pricing exist (2).

#### *1. Reimbursement*

In England, most licensed drugs that are prescribed in general practice, are automatically reimbursed except if they are integrated in one of the two negative lists based on the evaluations of the National Institute for Health and Care Excellence (NICE)<sup>10</sup>: the black list includes medicinal products that cannot be prescribed within the NHS, and the grey list

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<sup>9</sup> Article 2 of Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems [1989] OJ L40/p8.

<sup>10</sup> NICE was established in 1999.

includes medicinal products that can be prescribed by doctors within the NHS only for specific patients' groups and indications.<sup>11</sup> However, cell- based regenerative therapy generally involves surgical procedures (this is the case for ChondroCelect, MACI and Holoclar) or request particular conditions (an environment where resuscitation equipment is available must be ensured for the administration of Provenge; Holoclar and ChondroCelect are restricted to hospital use only). Consequently, these medicinal products should be administered in hospitals. But the black and grey lists that are provided for general practice do not apply to hospital doctors. Indeed, the latter are governed by their terms of employment with the hospital. Three main actors can be involved in the economics evaluation of cell-based regenerative therapies that will constitute the basis for decisions on reimbursement: the National Institute for Health Research Horizon Scanning Research & Intelligence Centre (NIHR HSRIC), NICE, and the NHS commissioning structures. The NIHR HSRIC, funded by the National Institute for Health Research, aims

to supply timely information to key policy- and decision-makers and research funders within the English National Health Service (NHS) about emerging health technologies that may have a significant impact on patients or the provision of health services in the near future.<sup>12</sup>

From 2008, this centre assessed regenerative medicine based technologies, notably ChondroCelect,<sup>13</sup> but its activity on this topic enhanced from 2010.<sup>14</sup> The NIHR HSRIC, located at Birmingham University, notifies NICE (normally 20 months before marketing authorisation for new drugs and 15 months before for new indications) on new and emerging health technologies that should be assessed by NICE.

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<sup>11</sup> National Health Service (General Medical Services Contracts) (Prescription Drugs) regulations 2004.

<sup>12</sup> NIHR HSRIC <<http://www.hsrhc.nihr.ac.uk/about-us/>>.

<sup>13</sup> NIHR, National Horizon Scanning Centre, ChondroCelect for knee cartilage defects, August 2008.

<sup>14</sup> Several reports have been published on this topic in the fields of ophtalmology (2012), neurological conditions (2012), musculoskeletal disorders (2013), cardiac diseases (2013), skin disease, burns and wound care (2014).



NICE is notably in charge of the evaluation of new drugs that will be available and reimbursed within the NHS.<sup>15</sup> However, such evaluation by NICE is not automatic. Indeed, there is a topic selection by NICE and Department of Health (DoH) based on the NIHR HSRIC opinions, a Department of Health request, and Manufacturers' applications. NICE's evaluation at national level is generally requested for new drugs with high price or with uncertain efficacy, two aspects that are generally shared by most of cell- based regenerative therapies. NICE's assessment is based on available evidences, and notably on the cost/effectiveness balance which includes the Quality Adjusted Life Year (QALY) analysis. This takes into account the impact of the treatment on the longevity and quality of life. It is linked to a threshold from £ 20.000 to £ 30. 000. It implies that if the NHS accepts to pay a new treatment, it will not pay another activity in that therapeutic area if it has a fixed budget.

If a new drug has a cost-per-QALY of 20.000£, then the QALYs gained by implementing the new drug will be approximately equal to the QALYs displaced elsewhere in the NHS ie there will be no net health benefit from using the new drug. If a new drug has a cost-per-QALY of less than 20.000£, then the QALYs gained by implementing the new drug will exceed the QALYs displaced elsewhere in the NHS ie a positive net health benefit arises from using the new drug.<sup>16</sup>

Although the QALY and this threshold have been widely criticized,<sup>17</sup> from January 2002, the NHS is legally bound to reimburse treatments that are recommended by NICE in the context of the technology appraisal procedure. However, guidance provided by NICE in the context of

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<sup>15</sup> NICE is also responsible for “producing evidence based guidance and advice for health, public health and social care practitioners, developing quality standards and performance metrics for those providing and commissioning health, public health and social care services, providing a range of informational services for commissioners, practitioners and managers across the spectrum of health and social care”. NICE website <<http://www.nice.org.uk/about/what-we-do>>.

<sup>16</sup> D Epstein, ‘Value based pricing of new pharmaceuticals in the United Kingdom National Health Service’ (2014) < <http://www.ugr.es/~davidepstein/notesVBP2.pdf>>.

<sup>17</sup> M Drummond, ‘What are the HTA processes in the UK?’, The NHS and HTA, What is...? Series (2009) <[http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/What\\_are\\_HTA\\_proc.pdf](http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/What_are_HTA_proc.pdf)>.

other evaluation procedures are not legally binding for the NHS.<sup>18</sup> Moreover, it should be noted even though there is a negative mandatory evaluation by NICE, manufacturers can sometimes negotiate a specific agreement with the government: reimbursement of a treatment in the context of its being research only, shared risks by linking price to drugs' performance, or financial agreement to control budget impact.<sup>19</sup> Manufacturers can also propose a Patient Access Scheme (PAS), i. e. a lower price or a dose upper limit. If such a scheme is agreed between the company and the DoH (with the involvement of the Patient Access Scheme Liaison Unit (PASLU) at NICE), the treatment will be re- assessed by NICE on the basis of this new price to ensure that its cost per QALY will be under the acceptable threshold.<sup>20</sup>

Without NICE formal binding assessment, i.e. without any evaluation by NICE or where NICE only provides non-binding recommendations, decisions will be taken by NHS commissioning structures. NHS England will take decision at national level for specialised services. The latter are those provided in relatively few specialist hospitals and accessed by a small number of patients. Such concentration of services aims to ensure an easier recruitment and training of specialist staff while providing the best use of human (staff expertise) and material (high tech equipment) resources<sup>21</sup>. Otherwise, in accordance with the Health and Social Care Act 2012, decisions are delegated to local clinical commissioning groups that have discretion in this matter.

In France, the reimbursement of a medicinal product relies on the principle of the inscription on a positive list. In French law, a distinction is made between the ambulatory pathway, i.e. medicinal products are accessible from pharmacies in the cities, and the hospital pathway, i.e.

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<sup>18</sup> L Nguyen- Kim, Z Or, V Paris, C. Sermet, 'The politics of drug reimbursement in England, France and Germany' (2005) 99 Issues in Health Economics 1, 5.

<sup>19</sup> D Epstein, Value based pricing of new pharmaceuticals in the United Kingdom National Health Service, *op. cit.* p4.

<sup>20</sup> *Ibid.* p5.

<sup>21</sup> NHS England, Manual for prescribed specialised services 2013/14, January 2014, p8.

medicinal products are accessible in health establishments<sup>22</sup> via what is called “pharmacies for internal use” (“Pharmacies à usage intérieur”)<sup>23</sup>. As mentioned above, the technicity of cell- based regenerative therapy generally implies they should be administered in hospitals. I will consequently focus on the hospital pathway.

The French law provides that only the medicinal products that are registered on the list of medicinal products that are authorised for use in regional authorities and diverse public services can be used in hospitals.<sup>24</sup> The registration of a medicinal product on this list is decided by legal order of the Health and French “social health insurance” Ministers. As long as a medicinal product is registered on this list it can be bought by health establishments and it will be reimbursed by the French social health insurance system. However, the drugs’ registration on this list does not ensure its supply by every local health establishments. Indeed, each one of them will decide to supply registered medicinal products or not.

In France, the marketing authorisation holder can engage an application with the High Authority for Health (Haute Autorité de Santé- HAS) to request the registration of its medicinal product on the list of medicinal products that are authorised for use in regional authorities and diverse public services, i. e. in hospitals.

Thus, regarding drugs’ reimbursement, England and France are generally different: the former excludes the hospital pathway from its system of negative lists (black and grey lists) and the drugs’ evaluations are made either at the national level (by NICE, or by NHS England for specialised services) or at the local levels by local clinical commissioning groups whereas the

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<sup>22</sup> Articles L6111-1 and following of the French Public Health Code provide the missions of the health establishments whatever their public or private statute. They have to ensure the diagnostic, control, and treatments of patients; to provide healthcare; to participate to the coordination of care with the healthcare professionals from the cities; to participate to the implementation of the health policy and vigilance systems for health safety; to have an ethical thinking on the medical care; to create and implement a policy to improve continuously the quality and safety of care and risk management to prevent and treat adverse effects linked to their activities; to struggle adverse effects notably; to define a policy for medicinal product and medical devices.

<sup>23</sup> M Aulois-Griot, F Taboulet, *Etablissements de santé, structures de tutelle et pharmacies à usage intérieur* (4th edn Wolters- Kluwer, Paris 2013) 453-466.

<sup>24</sup> Article L5123-2 of the French Public Health Code.

latter bases its system on positive lists for the hospital pathway and the drugs' evaluation are made both at the national (by the High Authority for Health- HAS) and local levels.

## 2. Pricing

In the UK, two regulatory schemes co-exist for drugs' pricing. First, companies can choose to join the Pharmaceutical Price Regulation Scheme (PPRS). The PPRS agreements are signed every five years between the industry, represented by the Association of the British Pharmaceutical Industry (ABPI), and the DoH for the supply of branded drugs to the NHS for England as well as for the devolved countries. The current 2014 PPRS has been implemented from 1 January 2014 and will terminate on 31 December 2018.<sup>25</sup> On the one hand, industrials freely set drugs' prices. On the other hand, they accept an *ex post* control of their profits and a global negotiation on prices. More specifically, the PPRS sets a maximal profit threshold beyond which pharmaceutical laboratories consent to modify their prices within the range of considered products. They are free to choose which products will be submitted to a price diminution as long as the global objective of price reduction established by the PPRS is respected. However, such a system has been criticized as it could incite industrials to set high prices to anticipate forthcoming diminution. Moreover, it would not sufficiently take into account the clinical effectiveness of drugs.<sup>26</sup> Second, where a company decides not to join the 2014 PPRS, it automatically falls under the Statutory Scheme that imposes a list price cut of 15% on products.<sup>27</sup>

While under the 2014 PPRS, the UK national competent authorities do not directly control prices but rather control profit, it is the contrary under the Statutory Scheme.<sup>28</sup> Although

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<sup>25</sup> Department of Health and Association for British Pharmaceutical Industry, the Pharmaceutical Price Regulation Scheme 2014, December 2013.

<sup>26</sup> Premier Ministre de la République française, Commissariat à la stratégie et à la prospective, 'La note d'analyse : les médicaments et leurs prix : comment les prix sont-ils déterminés ?' 10 (2014), 5 <<http://www.strategie.gouv.fr/sites/strategie.gouv.fr/files/archives/2014-03-04-Prixdumedicaments-NA101.pdf>>.

<sup>27</sup> The Health Service Medicines (Control of Prices and Supply of Information) (Amendment) Regulations 2013, Statutory Instrument No 2881.

<sup>28</sup> ABPI, Understanding the 2014 Pharmaceutical Price Regulation Scheme (2014) <[http://www.abpi.org.uk/our-work/policy-parliamentary/Documents/understanding\\_pprs2014.pdf](http://www.abpi.org.uk/our-work/policy-parliamentary/Documents/understanding_pprs2014.pdf)>.

companies can choose to be covered by the Statutory Scheme, most of them choose to join the PPRS. Cell- based regenerative therapies are not specifically considered in the 2014 PPRS yet. However, they may benefit from flexible pricing that

allows a company to propose an initial price for a technology that reflects value that can be demonstrated at launch, while retaining the freedom to apply to increase or decrease this original list price either as further evidence or as new indications emerge and change the effective value that the technology offers to NHS patients.<sup>29</sup>

It may be relevant in two circumstances according to the 2014 PPRS: significant new evidence that changes the value of an existing indication is generated and a significant new indication is proposed<sup>30</sup>.

In France, regarding pricing of drugs registered on the list of medicinal products that are authorised for use in regional authorities, the general regime is based on prices that are freely established by pharmaceutical companies and arranged with hospitals. However, drugs can be registered on a list of medicinal products that can be charged *in sus* than hospital services. In that case, those drugs prescribed to patients in hospitals are reimbursed on the basis of the so-called “responsibility tariff”, i. e. an upper limit price agreed between the enterprise and the health products economic Comity (“Comité économique des Produits de Santé”- CEPS).<sup>31</sup> This list called “*in sus* list”, established by ministerial order,<sup>32</sup> has been set up to avoid discordance and patients selection risks that could appear with the use of very expensive health products and to favour the spread of innovative medical technologies. Indeed, very expensive products would be factors of statistic heterogeneity in costs distribution: very high

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<sup>29</sup> NICE, ‘Guide to the processes of technology appraisal’, Process and methods guides (2014), 74.

<sup>30</sup> *Ibid.* pp80- 81.

<sup>31</sup> Where there is no agreement in a 180 days delay, the responsibility tariff is set up by the health products economic Comity. Nevertheless the concerned ministers (health, social health insurance and economics) can oppose to the decision of the health products economic Comity, and set this tariff. Article 162- 16- 6 of the French social health insurance code.

<sup>32</sup> This list is regularly updated and includes around a hundred of products.

cost of the product in comparison with the tariff of the concerned “diagnosis related group”<sup>33</sup>, or product supposed to be for a limited number of patients. Thus, it will be particularly relevant for cell- based regenerative therapies to come under such list. In that case, while pharmaceutical companies are free to set up the price of their drugs, the arrangements with hospitals on such prices are widely influenced by this “responsibility tariff”, which is the basis for the reimbursement by the national health insurance. Indeed, if a health establishment buys a drug that is on this list *in sus* for a price superior or equal to the responsibility tariff, the national health insurance will not reimburse more than the responsibility tariff. The surplus will be charged to the health establishment and not to the patient.<sup>34</sup> Nevertheless, if a health establishment buys a drug that is on this list *in sus* for a price inferior to the responsibility tariff, the basis for reimbursement by the national health insurance will include 50% of the difference between the purchase price and the responsibility tariff in addition to the purchase price of the medicinal product.<sup>35</sup> It permits a profit- sharing of the health establishment where it diminishes its expenses.

Thus, in France as in the United Kingdom (except under the Statutory Scheme), prices are freely set by companies and indirectly controlled by national authorities. Interestingly, even though France does not have a national strategy on regenerative medicine, it has a specific procedure for the pricing of innovative medical technologies and very expensive drugs, that would include cell- based regenerative therapies, with the *in sus* list. In such a general context, it is relevant to consider the regulatory pathways in which cell- based regenerative therapies are embedded for reimbursement.

### *B. Regulatory pathways for reimbursement of cell- based regenerative therapy in England and France*

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<sup>33</sup> The diagnosis- related group (“Groupe homogène de séjour”) is a basis for the main mode of financing of public and private health establishments.

<sup>34</sup> Article 162- 16- 6 of the French social health insurance code.

<sup>35</sup> Article 1, Legal Order of 9 May 2005 implementing part II of article L162-16-6 of the French social health insurance code, French OJ n°121 of 26 May 2005, page 9102, text n° 15.

Both in England and in France decisions on the reimbursement of cell- based regenerative therapy can be taken at the national (1) and/or at the local and mixed levels (2).

### *1. At the national levels*

Decisions on reimbursement of cell- based regenerative therapy rely on two main national regulatory agencies, respectively NICE in England and HAS in France. However, whereas multiple regulatory pathways can be relevant for cell- based regenerative therapy at NICE (a), only one exists at HAS (b).

#### *a. Multiple Regulatory Pathways at NICE in England*

Within NICE, two assessment procedures that result in binding obligations for NHS commissioning can be applied to innovative products, including cell- based regenerative therapies.

Firstly, Health Technology Assessment (HTA)<sup>36</sup> (or Health Technology appraisal)<sup>37</sup> is used for larger target populations. Such assessment can be either single ('single technology appraisal') when it covers only one technology for one indication, or multiple ('multiple technology appraisal') when it covers more than one technology or one technology for more than one indication. The NIHR HSRIC, individual healthcare professionals, NHS commissioners, DoH policy teams and manufacturers can contact NICE to suggest it assesses new health technologies through the HTA procedures.<sup>38</sup> But final decisions on which topics are referred to NICE for appraisal, are made by Ministers at the DoH.<sup>39</sup> The selection of technologies that will be assessed by NICE relies on selection,<sup>40</sup> elimination<sup>41</sup> and

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<sup>36</sup> The word 'technology' is used because this procedure can be applied to medicinal products, medical devices, diagnostic techniques, surgery procedures, and health promotion activities.

<sup>37</sup> Although the literature generally refers to 'Health Technology Assessment', NICE's wording is 'Technology appraisal'.

<sup>38</sup> NICE, 'Guide to the methods of technology appraisal' (2013) § 1. 2. 3.

<sup>39</sup> *Ibid.*

<sup>40</sup> The technology is likely to result in significant health benefit and impact on other health- related Government policies (i. e. reduction in health inequalities). NICE guidance is likely to add value as in its absence there could be uncertainty over clinical and cost effectiveness and variation in the use of the technology across the country.

<sup>41</sup> Are excluded: unlicensed technologies with no plan for licensing, modification to an existing formulation or technology, population screening, vaccination, HIV technology/therapy, technologies that are covered in existing

prioritisation (targeted population, disease severity, resource impact, and claimed therapeutic benefit over available NHS treatments)<sup>42</sup> criteria to filter topics and technologies that will be effectively assessed by NICE.<sup>43</sup> These evaluations are based on the analysis of clinical and economic evidences. NICE's methodology on health technology appraisal<sup>44</sup> has been recently completed by addendum based on a public consultation,<sup>45</sup> following the strengthening of the 'value' concept of new technologies.

Secondly, the Highly Specialised Technologies Evaluation (HSTE) is more appropriate for therapies for rare diseases. This procedure can be relevant for cell- based regenerative therapies that may obtain the orphan designation if the criteria are fulfilled as it has been for Holoclar on 7 November 2008. The implementation of this procedure relies on the following assessment criteria:

The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS (Originally defined as no more than 500 patients per annum); Highly unlikely there is a clinically meaningful alternative; The condition is chronic and severely disabling; The technology is likely to have a very high acquisition cost; The technology has the potential for life long use; The target patient group is distinct for clinical reasons (e.g. not for genetic reasons alone); The technology is expected to be used exclusively in

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guidance, technologies for which there is a lack of evidence, technologies which are not closed to be launched in timing, technologies that do not address key clinical questions. NICE, 'Technology appraisals topic selection' (2013).

<sup>42</sup> The prioritisation criteria rely on the following questions: "is the technology likely to result in a significant health benefit, taken across the NHS as a whole, if given to all patients for whom it is indicated? Is the technology likely to result in a significant impact on other health-related Government policies (for example, reduction in health inequalities)? Is the technology likely to have a significant impact on NHS resources (financial or other) if given to all patients for whom it is indicated? Is there significant inappropriate variation in the use of the technology across the country? Is the Institute likely to be able to add value by issuing national guidance? For example, in the absence of such guidance is there likely to be significant controversy over the interpretation or significance of the available evidence on clinical and cost effectiveness?" NICE, 'Guide to the process of technology appraisal', (2014) 2) Selection of technologies; and NICE, Centre for Health Technology Evaluation, 'Updated prioritization criteria for referral of technology appraisal topics to NICE' (2010).

<sup>43</sup> NICE, 'Guide to the process of technology appraisal' (2014).

<sup>44</sup> NICE, 'Guide to the methods of technology appraisal' (2013).

<sup>45</sup> There was a public consultation on this topic, opened from 27 March 2014 to 20 June 2014. NICE, 'Methods of technology appraisal consultation 2014'.



the context of a highly specialised service; The need for national commissioning is significant; Available data should permit undertaking of assessment.<sup>46</sup>

Moreover, another discretionary procedure that relies on NICE's recommendations could be relevant for the evaluation of cell-based regenerative therapies. Although NICE's recommendations are not mandatory regarding the reimbursement within the NHS, they can support decisions of NHS commissions. The so-called 'Interventional procedure' aims to assess the safety and efficacy of new<sup>47</sup> interventional procedures.<sup>48</sup> It does not take into account the cost or cost/effectiveness. This procedure results in NICE's recommendations according to the following four main types: 'normal arrangements',<sup>49</sup> 'special arrangements',<sup>50</sup> 'research only',<sup>51</sup> or 'should not be used',<sup>52</sup> regarding the technology assessed.<sup>53</sup> It should be noted that another procedure covers 'CE' medical devices that are

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<sup>46</sup> P Kefalas, 'Market access considerations for the cell therapy industry' (Cell Therapy Catapult, London, UK, March 2014) <<https://ct.catapult.org.uk/documents/10588/12779/UK+market+access+considerations+for+the+cell+therapy+industry.pdf>> accessed 18 February 2016; NICE, Interim process and methods of the highly specialised technologies programme, May 2013.

<sup>47</sup> "An interventional procedure should be considered new if it is not in regular use and a clinician, no longer in a training post, is using it for the first time in their [...] clinical practice. Whilst the Programme is concerned largely with new procedures, it may also assess established procedures if there is a concern about their safety and/or efficacy". Department of Health, Social Services and Public Safety, National Institute for Health and Care Excellence (NICE)- Interventional Procedures Programme, 4 March 2014, Circular HSC (SQSD) 4/14, p2.

<sup>48</sup> "Interventional procedures are those used for diagnosis or treatment that involve incision, puncture, entry into a body cavity or the use of ionising, electromagnetic or acoustic energy". NHS, NICE, Interventional Procedures Programme, Process Guide, January 2009, p5.

<sup>49</sup> Evidences should be valid, relevant and of good quality; available in sufficient quantities for the Committee to make a positive decision; sufficiently consistent in nature; demonstrate benefits with an appropriate time of the procedure; it should also be demonstrated that the frequency and severity of adverse effects of the procedure are similar to, or less than, those of any comparable and established procedures". NICE, Interventional Procedures Programme, Methods Guide, June 2007, p29.

<sup>50</sup> Where the conditions of 'normal arrangements' cannot be fulfilled, "recommendations are made for clinicians to use the procedure only with special arrangements for consent and/or audit and/or research. It is also stipulated that the clinical governance leads of trusts should be notified. This recommendation is often made when the procedure is considered to be emerging practice in the NHS". NICE, Interventional Procedures Programme, Methods Guide, June 2007, p30.

<sup>51</sup> This procedure "should be carried out only in the context of formal research studies approved by a research ethics committee". *Ibid.*

<sup>52</sup> This procedure 'should not be used' as "the evidence suggests that it has no efficacy and/or poses unacceptable safety risks". *Ibid.*

<sup>53</sup> NICE, Interventional Procedures Programme, Methods Guide, June 2007, p29- 30.

excluded from the scope of this article that focuses on medicinal products: the Medical technologies Guidance (MTEP).<sup>54</sup>

Finally, it should be recalled that without NICE formal assessment, decisions on reimbursement could be taken at national level by NHS England for specialised services commissioning. Indeed, NHS Specialised Services are managed by a national body, the NHS Commissioning Board, for commissioning services that relate to a small number of patients (usually less than 500 per year) in few UK hospitals.<sup>55</sup> However, as in practice, 10 Specialised Commissioning Groups commission specialised services typically provided in a very limited number of regions,<sup>56</sup> the tricky sharing between the NHS commissioning structures will be considered below at the local and ‘mixed’ level.

Whereas three regulatory pathways could be relevant for cell- based regenerative therapy at NICE, there is only one at the HAS in France.

#### *b. One single regulatory pathway at the High Authority for Health in France*

Within the HAS, which is an independent administrative authority, a specific commission called “the Transparency Commission”<sup>57</sup> is in charge of giving opinions on the basis of which the registration on the list of medicinal products that are authorised for use in regional authorities and diverse public services will be decided.<sup>58</sup>

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<sup>54</sup> NHS, NICE, Medical Technologies Evaluation Programme, Process guide and Methods guide, April 2011.

<sup>55</sup> The NHS Commissioning Board was established on 1st April 2013. NHS Commissioning Board, Specialised services commissioning transition team, Securing equity and excellence in commissioning specialized services, November 2012; and NHS England News, New national model to tackle variation in specialist healthcare services, 21 November 2012 <<https://www.england.nhs.uk/2012/11/spec-services/>> accessed 18 February 2016.

<sup>56</sup> NHS England News, NHS England launches major exercise to shape the future of specialised services, 6 November 2013.

<sup>57</sup> The Transparency Commission is composed of 20 permanent members (one president and one vice- president appointed by the Health and Social Health Insurance Ministers and 17 members are appointed for their scientific competences), 6 alternates with a deliberative vote, and 8 members with consultative vote (The general director for Health, the general director for the social health insurance, the general director of the General Direction for the offer of care, the general director of the French Agency for medicinal products, 3 persons representing the pharmaceutical industry (LEEM). Article R163- 15 of the French social health insurance code.

<sup>58</sup> It should be noted that another commission is in charge of the evaluation of medical devices and health technologies that are not legally considered as medicinal products for their reimbursement: “National Commission for the evaluation of medical devices and health technologies”.

For the registration on this list, rules and procedures are provided by the French Code of social health insurance. First, the Transparency Commission assessed the medical benefit (“Service Médical Rendu”- SMR) of each therapeutic indication of a medicinal product. This therapeutic indicator relies on the evaluation of five parameters: the efficacy and adverse effects of the drug, its place in the therapeutic strategy (i. e. its positioning compare to other therapeutic alternatives), the severity of the disease, the preventive, curative or the symptomatic character of the treatment, and the impact on public health (i. e. the impact of the drug on the population’s health regarding mortality, morbidity and quality of life; the impact on healthcare organisation and on the public health policy; and the ability of the drug to answer to a public health need not covered).<sup>59</sup> The analysis of these parameters permits to grade the medicinal product according to a medical benefit scale of 5 possible grades: from insufficient (= no registration on the list and no reimbursement), then poor to important (eligible for price negotiation). Then the Transparency Commission assesses the “Improvement of medical benefit” or “Therapeutic added value” (“Amélioration du Service Médical Rendu”- ASMR) to determine the significance of the therapeutic progress provided by the drug in comparison with other health products of the same therapeutic class. The improvement of medical benefit is graded from I to V with a positive opinion for the registration on the list: I for the major therapeutic progress, II for a significant improvement regarding the therapeutic efficacy and/or the diminution of adverse effects, III for a modest improvement regarding the therapeutic efficacy and/or the diminution of adverse effects, IV for a minor improvement regarding the therapeutic efficacy and/or the clinical utility, and V for no improvement.<sup>60</sup>

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<sup>59</sup> Article R163-3 of the French social health insurance code.

<sup>60</sup> Article R163-5 of the French social health insurance code.

This medico-administrative or medico- technical evaluation<sup>61</sup> by the Transparency Commission ends up with the publication of an opinion from this Commission, the so- called “Transparency opinion”, accessible online on the HAS’s website. It includes multiple information regarding the medicinal product especially the medical benefit and the improvement of medical benefit.<sup>62</sup> On the basis of this opinion, the Minister of health and French “social health insurance” decides whether to register the medicinal product on the list of medicinal products that are authorised for use in regional authorities. It should be underlined that drugs which do not have a sufficient improvement of medical benefit and which do not give rise to a diminution in the cost of treatment cannot be registered on the list of medicinal products that can be reimbursed in the towns’ pharmacies pathway.

Although multiple potential pathways exist at NICE for the evaluation of drugs, and a single regulatory pathway at the HAS which in any case is completed by local evaluations, none of them is specific to cell- based regenerative therapy.

## *2. At the local and mixed levels*

In England, NHS Commissioning structures are “the budget holders for the health economy and will commission services at local, regional, or national level from a wide range of providers”.<sup>63</sup> As said above, NHS legally has to fund and provide treatments recommended by NICE’s technology appraisal (either single or multiple under TA or under HSTE). However, all therapies cannot be assessed by NICE because of capacity constraints and selection criteria as explained above. In these cases without NICE formal assessment, NHS will decide on commissioning for therapies either at the national level for specialised services through the 10

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<sup>61</sup> The 2014 press file of the HAS uses the expressions « medico- technic criteria » and « medico- technic file » regarding the evaluation and the application to the Transparency Commission. French HAS, Press file, Press conference on 29 September 2014, [Health system regulation by quality and efficiency], p3.

<sup>62</sup> According to article R163- 18 of the French social health insurance code, the transparency opinion gives information on the legitimacy of the registration regarding the medical benefit assessed for each therapeutic indication, the improvement of medical benefit assessed for each therapeutic indication in the therapeutic class of the product regarding three comparators (drug the most sold, the most costly, and the last registered), the conditions for the use of the drug, the targeted population, the rate for reimbursement, the match with packaging

<sup>63</sup> VALUE project Final report, Regenerative Medicine: Navigating the uncertainties, March 2012, p21.

regional specialised commissioning groups or at the local level for other services through the 209 clinical commissioning groups. It should also be noted that if five or more “individual patient request” are made by clinicians through a formal procedure for a new technology, NHS England has to produce a commissioning policy for it as a clinical service at one or more providing centres. Where therapies appear in the Manual for prescribed specialised services,<sup>64</sup> commissioning decisions are taken by NHS Specialised Services. For all the other therapies, commissioning decisions are taken by local Clinical Commissioning Groups that have discretion in this matter. The lack of transparency regarding the methodologies and criteria used to decide on reimbursement at the local level combined to the multiple responsible Clinical Commissioning Groups contribute to the obscurity of the system. Hence, the national homogeneity provided for specialised services is opposite to the huge variations occurring for all other services. At the moment, cell- based regenerative therapies as defined in this paper are not in the Manual; decisions on their reimbursement consequently falls under the remit of local Clinical Commissioning Groups where there is no previous mandatory NICE decision. They could be included in the Manual in the future by Ministerial decision following an opinion from a committee called the Prescribed Specialised Services Advisory Group. In such a context, four factors determine whether NHS England will commission a therapy as a specialised service: number of individuals who require provision of service (size of target population), cost of providing the service or facility, number of persons (clinicians/hospitals) able to provide the service or facility, financial implications for Clinical Commissioning Groups if they were required to commission the service of facility themselves.<sup>65</sup> NHS Specialised Services are advised by Clinical Reference Groups and/ or by the Rare Diseases Advisory Group. The latter group receives recommendations from Clinical Reference Groups and formulate its advice on the basis of evidence from professional bodies and patient

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<sup>64</sup> NHS England, Manual for Prescribed Specialised Services 2013/14, January 2014.

<sup>65</sup> NHS Commissioning Board, Specialised services commissioning transition team, Securing equity and excellence in commissioning specialized services, November 2012, *op. cit.* p4.

groups.<sup>66</sup> It also makes recommendations to NHS England, NHS Scotland, NHS Wales and NHS Northern Ireland on developing and implementing the strategy for rare diseases and highly specialised services.<sup>67</sup> In such a context, NHS England set up a working group on regenerative medicine and the RMEG report recommended to formalise it into a Clinical Reference Group for regenerative medicine.<sup>68</sup> However, the latter is not yet set up and unlikely to be so. Finally, it should be noted that for unlicensed therapies, commissions decisions should be taken on the basis of NICE ‘Evidence Summaries’<sup>69</sup> and decentralised at the level of NHS local commissioners.<sup>70</sup>

In France, at the local levels within each health establishment, the so- called medical Commission of establishment<sup>71</sup> sets up, on the basis of the list of medicinal products that are authorised for use in regional authorities, a list of medicinal products that will be available in the pharmacy for internal use and that are recommended by the establishment. In 2005, a study by B. Juillard- Condat et al. on the Toulouse university hospital notably highlighted that only 43, 2 % of medicinal products referenced within the establishment had an accessible opinion from the Transparency Commission.<sup>72</sup> Among them, the level of the medical benefit has been explicitly assessed in 98, 1% of the opinions of the Transparency Commission (93% has an important medical benefit) whereas the improvement of medical benefit has been

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<sup>66</sup> NHS England, Rare Diseases Advisory Group: terms of reference, June 2013.

<sup>67</sup> *Ibid.*

<sup>68</sup> RMEG, *op. cit.* p17.

<sup>69</sup> Evidence summaries are not formal NICE guidance but they “help commissioners, budget holders and groups such as Area Prescribing Committees make informed decisions and aid local planning on the introduction of key new medicines. They are quality- assured summaries of the best available evidence for selected new medicines, or existing medicines with new indications or a new formulation, considered to be significant to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed, and a value assessment of each medicine is made based on its safety, effectiveness, patient factors and resource implications”. NICE, Evidence summaries, new medicines : < <http://www.nice.org.uk/about/what-we-do/our-programmes/nice-advice/evidence-summaries-new-medicines>>.

<sup>70</sup> J Jorgensen, P Kefalas, ‘Reimbursement of licensed cell and gene therapies across the major European healthcare markets’ (2015) 3 Journal of Market Access & Health Policy, 29321.

<sup>71</sup> This Commission was formerly called the Commission of medicinal product and sterile medical devices. The law n°2009-879 of 21 July 2009 reforming the hospital and relating to patients, health and territories (French OJ n°0167 of 22 July 2009, page 12184, text n°1) leaves the medicinal product policy to the medical Commission of establishment.

<sup>72</sup> B Juillard- Condat, MC Durand, F Taboulet, ‘SMR et ASMR : quelle utilité dans le contexte hospitalier ?’ (2008) 26 Journal d’Economie Médicale, 269-282.

assessed only for 16% of the referenced medicinal products (17% had a level I or II improvement of medical benefit, 15% a level III, 13% a level IV, and 38% a level V). This study notably raised the problems related to the lack of availability of the Transparency Commission's opinions and their lack of updates. But since 2005, the HAS has a permanent preoccupation for transparency in all its activities. Consequently, the opinions of the Transparency Commission are much more complete and more frequently available online on its website.<sup>73</sup>

Thus, even though several pathways exist for cell- based regenerative therapies at NICE, only two (the TA and HSTE) result in binding obligations for NHS commissioning. It implies that where a cell- based regenerative therapy is submitted to another pathway at NICE, or is not considered at the NICE level, the decision to reimburse it or not and to supply it or not within the NHS can be different at the local levels as they fall under the remit of NHS Commissioners (as long as they are not included in the Manual of Specialised services). The navigation between these different pathways and different institutions is complicated and their borders are not always clear. However, NICE recently established an 'Office for Market Access'

to provide companies with a 'flight path' through the stages of the development, evaluation and adoption of their products into the NHS; agreement between NICE, NHS England and the Department of Health, on the NHS's willingness to pay for new treatments, which would take account of any special cases, such as ultra-orphan conditions and cancer; more productive sharing of risk between companies and the NHS.<sup>74</sup>

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<sup>73</sup> HAS, Open data: [the French High Authority for Health publishes new data], Press release, 10 July 2014.

<sup>74</sup> NICE, Press release, NICE calls for a new approach to managing the entry of drugs into the NHS, 18 September 2014, *op. cit.*

In France, even though the criteria of medical benefit and improvement of medical benefit do not seem to be adapted to the local level of the hospital pathway,<sup>75</sup> the main barriers of the patients' access to authorised medicinal products come from the selection in each health establishment because of budget limitations which are quite obscure. Indeed, as specified above, after the centralised evaluation, there is always a decentralised evaluation in France.

Finally, England and France have different general legal frameworks for reimbursement and none of them is specific to cell- based regenerative therapy. However, the obscurity at the local levels characterised the two systems. Moreover, both countries have to address the reimbursement challenges raised by the assessment of cell- based regenerative therapy for their adoption in clinics.

### III- ADDRESSING CELL- BASED REGENERATIVE THERAPY'S REIMBURSEMENT CHALLENGES IN A CHANGING ENVIRONMENT

Both England and France have to address health budget limitations for aging populations. Growing pressures for the best use of limited resources necessitates the need to find the right methods to decide which treatments should be reimbursed by the national systems. Hence, the specificities of regenerative therapies, mainly its high up front cost and its potential curing effect should be considered in the assessment for decision on reimbursement. In such context, both countries have different trends towards the modification of their assessment for reimbursement, and their links to regenerative therapies (A). However, the assessments of the first cell- based regenerative therapy that obtained a European marketing authorisation, ChondroCelect for the treatment of knee cartilage provide similar outcomes in England and France (B).

#### *A. Different trends towards the assessment's modification for reimbursement*

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<sup>75</sup> B Juillard- Condat et al., 'SMR et ASMR : quelle utilité dans le contexte hospitalier ?', *op. cit.* p269-282.



The two main challenges for the reimbursement of cell- based regenerative therapies come from two specificities of these products: their potential curing effect and their high up front cost. On the one hand, the potential curing effect implies that the long- term benefit of using cell- based regenerative therapies, and consequently their impact on public health widely, should be taken into account in the evaluations to decide on their reimbursement (1). On the other hand, the high up front cost implies the impact on health budgets through the choices among the available treatments should be taken into account in the economics evaluations for decisions on reimbursement (2).

### *1. Strengthening the assessment of the public health value*

Thanks to the establishment of NICE, England has a long experience with the economics evaluation of drugs. However, the discussion's emphasis is now on how to take into account the wider value of health products for public health. First, England has been recently reforming pricing regulation and drugs assessments to focus its system on the concept of 'value- based pricing' regarding drug in general. Such reform, established by the Health and Social Care Act 2012, is ongoing from 2014. Value- based pricing links drugs and healthcare reimbursement to an evaluation based on evidences of value for patients, relatives, and the society.<sup>76</sup> It relies on a wider meaning of 'value' that includes three elements: the wider economic benefit,<sup>77</sup> the unmet need or burden of the disease,<sup>78</sup> and the therapeutic innovation and improvement.<sup>79</sup>

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<sup>76</sup> J Raftery, 'Value based pricing: can it work?' (2003) BMJ, 347.

<sup>77</sup> The wider economic benefit might include impact on direct costs and benefits of care that impact on patients but do not fall on the NHS budget (unpaid carers time, patients out of pocket expenses, quicker return to work, lost leisure time in accessing care), and indirect external effects (costs and benefits) on the rest of the economy (productivity gains). K Claxton, M Sculpher, S Carroll, 'Value-based pricing for pharmaceuticals: Its role, specification and prospects in a newly devolved NHS' (2011) Center for Health Economics, Research paper 60, 18- 19.

<sup>78</sup> This criterion relies on taking into account other aspects of social value that are not fully reflected in the measure of health gain used in the present NICE appraisal via QALY. "For example, QALY gains in areas where the burden of the disease is regarded as more severe (which might be defined in terms of current health, or past health experience, or the length and quality of life expected to be lost as a consequence of the condition) or rare (orphan drugs) might be regarded as more socially valuable and carry greater weight. This would allow

Whereas the value based pricing system should have been implemented in 2014, debates moved toward a new system of ‘value- based assessment’ (VbA). In June 2013, the Government requested NICE to undertake assessment based on value and did not request any other change. In such context, the cost/effectiveness threshold from £20 000 à £30 000 is maintained within the new PPRS 2014 and enterprises can always set prices of their new drugs although the total amount of drugs expenses is controlled.<sup>80</sup> NICE opened a public consultation on VbA of health technologies.<sup>81</sup> The VbA takes into account more specifically and explicitly the severity and the effects of the disease on people’s ability to be part of the society.<sup>82</sup> 900 comments from 121 organisations and individuals were received, and NICE decided that supplementary works were necessary before changing its evaluation method,<sup>83</sup> especially as it appears its board could not agree on the changes to be proposed. Second, although this general reform has turned down because of the difficulty knowing how to measure “value”, supplementary work on this aspect has started in the field of regenerative medicine specifically. Indeed, in March 2015, the RMEG report provided that applying NICE’s appraisal methodology,

based on cost utility analysis, to products whose true value may not be known for many years can be challenging, due to the inherent uncertainty of estimating long-term benefit from evidence derived from short-term studies.<sup>84</sup>

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medicines with these characteristics to be accepted with higher prices”. D Epstein, ‘Value based pricing of new pharmaceuticals in the United Kingdom National Health Service’, *op. cit.* p8.

<sup>79</sup> This criterion is based on the evaluation of the significant improvement brought by a new drug compare to existing treatments. Department of Health, A new value- based approach to the pricing of branded medicines- A consultation, 16 December 2010, p15.

<sup>80</sup> PPRS heads of agreement, 6 November 2013. D Cressey, ‘UK backs away from ‘value based pricing for drugs’ (2013) Nature News Blog.

<sup>81</sup> NICE, Centre for Health Technology Evaluation, Consultation paper, value based assessment of Health Technologies, 27 March 2014.

<sup>82</sup> *Ibid.*

<sup>83</sup> NICE, Press release, NICE calls for a new approach to managing the entry of drugs into the NHS, 18 September 2014.

<sup>84</sup> RMEG, Building on our own potential: a UK pathway for regenerative medicine, *op. cit.* p6.

Thus, it endorsed NICE's proposal "to undertake one or two 'mock' technology appraisal studies, on exemplar regenerative medicine products"<sup>85</sup> and encourage it "to consider the findings from these studies with a view to assessing whether changes to its methods and processes are needed".<sup>86</sup> This project started on April 2015 for an 8 months period and notably aims to identify key assessments needed regarding the value of regenerative medicine taking into account its potential curative nature and the claims of long- term/lifetime benefits.<sup>87</sup>

Both the general discussion on the value- based assessment and the mock appraisal for regenerative medicine can be considered as a trend towards strengthening the value of drugs for public health, with particular relevance for cell- based regenerative therapies. In that context, it may be useful for England to be learning from the French system that places the emphasis on the impact on public health rather than on economics evaluation. Firstly, the reimbursement on the basis of the responsibility tariff regarding the *in sus* list could be a procedure to be explored in England to enhance patients' equity in the access to cell- based regenerative therapies while considering their high cost. However, it should be adapted as the French's experience showed such incentive for the diminution of drugs' prices might become obsolete if managed as in France. Indeed, in France, the price diminutions agreed by the pharmaceutical companies led to a diminution of the responsibility tariff set up by the CEPS and consequently to a loss for the companies which would have accepted to not exceed a responsibility tariff always lower for hospitals to buy their drugs. Secondly, England could learn from the French Transparency Commission's evaluations that use criteria similar to those discussed in the context of the value- based pricing/assessment. Indeed, the curative character of the treatment, the severity of the disease and the impact on public health to assess

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<sup>85</sup> *Ibid.* p15.

<sup>86</sup> *Ibid.* p26.

<sup>87</sup> CRD/CHE University of York Research Protocol, Exploring the assessment and appraisal of regenerative medicines and cell therapy products, 8th June 2015.

the “medical benefit” and the assessment of the “Improvement of the medical benefit” echo the wider economic benefit, the unmet need or burden of the disease and the therapeutic innovation and improvement. They are also particularly relevant for cell- based regenerative therapies regarding their potential curative nature and their long- term benefit. However, as the French experience shows, caution is needed. On the one hand, the assessment of the “improvement of medical benefit” as in France appear to be limited for the local level where the following criteria need to be considered: the paediatric forms, the characteristics that may improve the observance, the high doses, the drugs associations or forms that facilitate the administration or the continuity of the treatment, and the necessity for therapeutic alternatives.<sup>88</sup> On the other hand, the President of the French HAS has appealed to merge the assessments of the “medical benefit” and the “improvement of medical benefit” to address the needs of comparative evaluation and criteria’s clarifications for costly therapeutic innovations.<sup>89</sup>

## *2. Strengthening the assessment of the economics value*

Contrary to England, France has no experience with the economics evaluation of drugs. Indeed, in France, the Transparency Commission carries out a ‘medico- technical’ evaluation only, it does not take into account the economics value of drugs. The medico- economic evaluation is under the remit of the economic evaluation and public health Commission (“Commission Evaluation Economique et de Santé Publique”- CEESP).<sup>90</sup> The latter has been established to provide an answer to the mission given to the HAS by the 2008 law for the financing of the national health insurance.<sup>91</sup> Henceforth the HAS can publish recommendations and medico- economic opinions on the most efficient care, prescription or

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<sup>88</sup> B Juillard- Condat et al., ‘SMR et ASMR : quelle utilité dans le contexte hospitalier ?’, *op. cit.* p280.

<sup>89</sup> HAS, Communiqué de presse du 29 septembre 2014; HAS, Activity Report 2013, *op. cit.* p94.

<sup>90</sup> This Commission met for the first time the 1st July 2008.

<sup>91</sup> Article 41 of the law n° 2007-1786 of 19 December 2007 the financing of the national health insurance for 2008, French OJ n°0296, 21 December 2007, page 20603, text n° 1.

reimbursement strategies. The 2008 law for the financing of the national health insurance<sup>92</sup> strengthened this mission making it mandatory under specific conditions. It fixes at the legislative level the medico- economic evaluation based on the efficiency criterion, i. e. the cost/efficacy balance of a drug. The Decree n°2012- 1116 regarding the medico- economic missions of the HAS, enforceable one year after its publication, i. e. since the 4 October 2013, specifies the conditions for the implementation of the medico- economic evaluation.<sup>93</sup> This evaluation is undertaken when the applicant claims a health product has a major, important or moderate improvement of the medical benefit or improvement of the benefit (ASMR I, II or III) and when it can have a significant impact on the national health insurance expenses.<sup>94</sup> These two cumulative conditions make obligatory the medico- economic evaluation when there is an application for registration on the reimbursement lists or for its renewal. The HAS has to define and make available to the public the conditions and criteria enforceable for the medico- economic evaluation.<sup>95</sup> The latter have recently been identified. As the “significant impact on the national health insurance expenses” criterion is vague, it has been discussed by the economic evaluation and public health Commission that firstly considered an easy decision’s rule should be proposed, with possibility for further evolution, to permit industrials to determine easily whether their products have to be submitted to the medico- economic evaluation. Criteria to be chosen should be “objective, easy and not manipulable”.<sup>96</sup> By decision of 18 September 2013, the HAS has specified the procedure to determine the “significant impact on the national health insurance expenses”.<sup>97</sup> The HAS examines the

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<sup>92</sup> Law n° 2011-1906 of 21 December 2011 on the financing of the national health insurance for 2012, French OJ n°0296, 22 December 2011, page 21682, text n° 1.

<sup>93</sup> Legal Decree n° 2012-1116 of 2 October 2012 on the medico- economic missions of the High Authority for Health, French OJ n°0231, 4 October 2012 page 15522, text n° 8.

<sup>94</sup> Article R161-71-1. - I. of the French social health insurance code.

<sup>95</sup> Article R161-71 4° b) of the French social health insurance code.

<sup>96</sup> CEESP, Meeting report, 14 May 2013, p6.

<sup>97</sup> HAS, Decision n°2013-0111 DC/SEESP of 18 September 2013 on the significant impact on the national health insurance expenses for the start of the medico- economic evaluation with a level I, II or III improvement of medical benefit, French Official Bulletin on Health, Social protection, and Solidarity n°2013/10, 15 November 2013, p1.

industrial company's claims regarding the impact of the product on the organisation of care, the professional practices or the conditions for taking charge of patients. It also takes into account the estimated turnover<sup>98</sup> of this product for all its therapeutic indications.<sup>99</sup> Where the industrial companies do not have specific claims, the HAS considers the medico- economic evaluation is requested as soon as the product's turnover is superior or equal top 20 million euros per year.<sup>100</sup> Moreover, the opinion of the CEESP on the foreseeable or observed efficiency for the reimbursement of the product, the so- called "efficiency opinion" is based on the comparative analysis of the balance between the engaged costs and the expected or observed benefits for the health and quality of life of the concerned persons regarding the different therapeutic alternative medically relevant.<sup>101</sup> On 18 December 2014, 15 efficiency opinions have been adopted among the 26 (25 medicinal products and 1 medical device) qualified for such procedure. In accordance with the national health insurance code, the HAS had to define and publish the medico- economic evaluation's methodologies adapted to the different preventive and care activities taking into account efficacy, quality, safety, prevention and care costs and organisation and their interest for public health, patients' quality of life, the improvement of the equal access to prevention and care, and the respect of ethical principles.<sup>102</sup> To this end, it adopted a guide on the methodological choices for the medico- economic evaluation by the HAS.<sup>103</sup> It provides 20 recommendations for a reference analysis that takes on two methods for the economic assessment: the cost-utility analysis<sup>104</sup> or the cost-

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<sup>98</sup> [The turnover of a product is the foreseen turnover every taxes included after two years of commercialisation where there is a first registration or the observed turnover every taxes included in case of registration renewal]. Article 1 alinea 2 of the HAS' decision n°2013-0111 DC/SEESP, *Ibid*.

<sup>99</sup> *Ibid*.

<sup>100</sup> Article 2 alinea 2 of the HAS' decision n°2013-0111 DC/SEESP, *op. cit*.

<sup>101</sup> Article R161-71-1. - II. of the French social health insurance code.

<sup>102</sup> Article R161- 71 4° a) of the French social health insurance code.

<sup>103</sup> HAS, economic evaluation and public health Department, methodological guide- methodological choices for the medico- economic evaluation by the HAS, October 2011.

<sup>104</sup> For the cost- utility analysis, the result criterion to be preferred if the lifetime adjusted to the quality. This analysis is systematically conducted with a cost- efficacy analysis that relies on the lifetime without moderation as a result criterion. *Ibid*. p18.

efficacy<sup>105</sup> analysis chosen according to the nature of the interventions' effects on health.<sup>106</sup> Finally, it should be noted that the efficiency opinion of the CEESP are public, submitted to a contradictory procedure, and transferred to the health products economic Comity. Thus in France, the HAS, via the CEESP, is in charge of the setting up and the diffusion of recommendations and medico- economic opinions on the most efficient strategies for prevention, healthcare, medical prescription or reimbursement and to participate to their comparison or organisation into a hierarchy in a public health and health insurance expenses' optimization objective.<sup>107</sup> Experience is still lacking regarding this medico- economic evaluation that was in a pilot phase in 2013.<sup>108</sup> However, two comments can be made regarding the French medico- economic evaluation and its use for regenerative therapies. First, it can be thought that products based on regenerative medicine will be submitted to this mandatory medico- economic evaluation because of their costs foreseen as high as long as they have a satisfying medical benefit or improvement of medical benefit (ASMR I, II or III). However, among the 7 efficiency opinions that have been published on the HAS's website on 25 August 2015, none of them is related to regenerative therapy yet. Second, the medico- economic evaluation is not necessarily taken into account for decision- making as long as an applicant's claim of ASMR I, II or III does not imply *ipso facto* such ASMR I, II or III will be granted by the Transparency Commission.<sup>109</sup>

Thus, two opposite trends appear. On the one hand, England, strong from its experience with economics assessment, is now trying to move towards a wider assessment that includes value for public health. On the opposite, France that was used to assess the impact of health

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<sup>105</sup> For the cost- efficacy analysis, the result criterion to be preferred is the lifetime. *Ibid.*

<sup>106</sup> The cost- utility analysis is preferred if the quality of life is a significant consequence. Otherwise the cost- efficacy analysis is preferred.

<sup>107</sup> Article R161-71 4° of the French social health insurance code.

<sup>108</sup> HAS, 2013 Activity Report, p20.

<sup>109</sup> C Rémuzat, M Toumi, B Falissard, 'New drug regulations in France: what are the impacts on market access? Part 2 impacts on market access and impacts for the pharmaceutical industry' (2013) 1 J Market Access Health Policy, 20892.

products on public health is now starting the economics assessment. These two trends are particularly relevant to address the challenges raised by the reimbursement of cell- based regenerative therapies. Both countries should be learning from each other experiences to go further in their respective trends. Their achievement would bring more convergence between the English and the French systems. Moreover, the English experience with NICE combined with the national strategy on regenerative medicine gives rise to specific thoughts such as the RMEG report, and activities such as the mock appraisal, for the thinking and the potential adaptation of methodologies for the decisions on cell- based regenerative therapies reimbursement. Such thinking is currently totally absent in France, although as the latter is logically working first on the setting- up and the improvement of the new general medico- economic evaluation. Moreover, while the Health Technology Appraisals at NICE determine the reimbursement and the availability in the NHS, the medico- economic evaluation in France is used for the negotiations on pricing by the CEPS without being directly linked to the decision- making on reimbursement.<sup>110</sup> Finally, contrary to England, there is not an explicit interpretation rule, nor a reference threshold in France to assess the efficiency of a health product. It should be noted that Toumi M. et al. considers

The French threshold exists intuitively but not as a hard value. Furthermore, it is not a key driver, as in the UK, but is instead modulated by a number of attributes, which not all are fully explicit. The French threshold ranges from £50,000 per QALY to as high as £300,000 per QALY for some rare conditions or oncology drugs. There is a clear perception that the French informal moving threshold may be outstandingly high compared to that of other countries.<sup>111</sup>

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<sup>110</sup> Inspection Générale des Affaires Sociales, Evaluation médico- économique en santé, Décembre 2014, p3.

<sup>111</sup> M Toumi et al., ‘Current process and future path for health economic assessment of pharmaceuticals in France’ (2015) *Journal of Market Access & Health Policy* [S.l.] v. 3.



In any case, such difference regarding the explicit definition of a reference threshold significantly highlights the lack of literature consensus on its necessity for decision-makers.<sup>112</sup>

Beyond such current differences between the two systems, the national assessments of the first cell- based regenerative therapy that obtained a European marketing authorization to treat the knee cartilage injury gave rise to similar outcomes: its non-reimbursement in France and England.

*B. The assessment of the treatment of knee cartilage injury: A similar outcome in  
England and France*

In England, the treatment of knee cartilage injury gave rise to two interventional procedures assessments that are not mandatory. In 2006, NICE considered mosaicplasty for knee cartilage injury had efficacy evidences for short term, but long-term efficacy data were inappropriate. Because of such efficacy uncertainties, NICE did not recommend mosaicplasty without specific measures being implemented.<sup>113</sup> The same occurred in 2012 regarding the partial replacement of the meniscus of the knee using a biodegradable scaffold.<sup>114</sup> Although these two decisions were discretionary as they come from interventional procedures assessments that are non-binding, the same position was followed by NICE within the context of technology appraisal that results in a mandatory decision. Indeed, the autologous chondrocyte implantation to treat cartilage injury was assessed by NICE in 2005, prior to the marketing authorisation of ChondroCelect. NICE did not recommend autologous chondrocyte implantation for the treatment of cartilage defects of the knee except for ongoing or new clinical studies “that are designed to generate robust and relevant outcome data, including the

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<sup>112</sup> HAS, Valeurs de référence pour l'évaluation économique en santé, Document de travail, Revue de la littérature, décembre 2014, p30.

<sup>113</sup> NICE, Mosaicplasty for knee cartilage defects, March 2006, Interventional Procedure n°162.

<sup>114</sup> NICE, Partial replacement of the meniscus of the knee using a biodegradable scaffold, July 2012, Interventional Procedure n°430.

measurement of health-related quality of life and long-term follow-up”.<sup>115</sup> A review of this appraisal is ongoing within NICE. It is a multiple technology appraisal that covers both ChondroCelet and MACI.<sup>116</sup> A single technology appraisal for ChondroCelet is also ongoing within NICE.<sup>117</sup> Consequently as NICE did not complete its assessment of ChondroCelet, the latter is not reimbursed within the NHS at the national level. However according to Tigenix, two Primary Care Trusts<sup>118</sup> would have accepted to fund ChondroCelet for individual requests.<sup>119</sup> In the private sector, according to Tigenix, two of the largest private health insurance in the UK would reimburse ChondroCelet.<sup>120</sup> Our researches confirmed BUPA was one,<sup>121</sup> but the second private insurance that would cover ChondroCelet in the UK has not been founded. Finally, it should be noticed that a UK private hospital, The Grosvenor Hospital in Chester, is proposing autologous chondrocyte implantation to its patients: it is offering ChondroCelet while specifying that this treatment is outside the NHS and NICE guidance, but that “NICE guidance does not override the responsibility of health professionals to make appropriate decisions on the circumstances of individual patients”.<sup>122</sup>

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<sup>115</sup> “Patients should be fully informed of the uncertainties about the long-term effectiveness and the potential adverse effects of this procedure”. NICE, Autologous chondrocyte implantation (ACI) for the treatment of cartilage injury, May 2005, Technology appraisal n°89. This appraisal was a review of an appraisal from 2000 (Technology appraisal n°16).

<sup>116</sup> The appraisal also covers OsCell cultured chondrocytes that are not commercially available as they do not have a marketing authorisation. NICE, Multiple technology appraisal, Final scope for the appraisal of autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89), Appendix B, May 2014. NICE consulted several stakeholders to comment its appraisal’s project. NICE, Multiple technology appraisal, Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89), Response to consultee and commentator comments on the draft remit and draft scope (pre-referral), Summary form, May 2014.

<sup>117</sup> NICE, Provisional matrix for the proposed single technology appraisal of ChondroCelet for repairing articular cartilage defects of the knee [ID686], pre-referral, June 2013.

<sup>118</sup> ‘Primary Care Trusts’ were local administrative health agencies that are part of NHS England. They managed healthcare providing by NHS hospitals, primary care centres, opticians, dentists, and pharmacists. They were abolished on 31 March 2013, following the entry into force of the Health and Social Care Act 2012. From 1<sup>st</sup> April 2013, they have been replaced by ‘clinical commissioning groups’.

<sup>119</sup> Tigenix, Annual report 2013, p40.

<sup>120</sup> *Ibid.*

<sup>121</sup> BUPA <<http://www.bupa.co.uk/>>.

<sup>122</sup> Chester Knee Clinic & Cartilage Repair Centre, Nuffield Health, The Grosvenor Hospital Chester, Tigenix ChondroCelet: Characterised chondrocyte implantation (CCI) for articular cartilage repair, Patient and General Practitioner Information, p3 <<http://www.kneeclinic.info/download/CKCTGXCCIPatientGPInfo150111.pdf>>.

Furthermore, it is involved in a clinical trial aiming to compare autologous chondrocyte implantation with MACI.<sup>123</sup>

In France, the Transparency Commission has examined the therapeutic interest of ChondroCelect. In its opinion from 6 October 2010, the following conclusions appear:

Even though the Commission considers it is an innovative biotechnology, the medical benefit should be provisionally considered insufficient on the basis of the present data to justify a reimbursement. The Commission cannot assess its therapeutic interest, especially to prevent arthrosis in the long term.<sup>124</sup>

This evaluation's result is based on two main arguments. On the one hand, the Commission considered that at the date of the application for reimbursement the clinical efficacy of ChondroCelect was not established notably regarding the size of the effect, the impact on the quality of life, the preventive effect on the development of the arthrosis of the knee.<sup>125</sup> The robustness of the results was considered arguable and the clinical superiority compare to the microfracture technic was not proved. On the other hand, a public health interest was not expected from ChondroCelect as long as its impact on the functional limitations and on the quality of life could not be established: according to the Commission, the file had no element on the long term prevention of arthrosis, available data came from only one study with a limited number of patients (112 patients among whom 51 have been treated with ChondroCelect and 61 by the microfracture technic), the transposable character of the results of the pilot trial to the practice was not ensured (numerous criteria for exclusion and necessity for the patients to follow a re-education program).<sup>126</sup> The evaluation process for the

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<sup>123</sup> The Grosvenor Nuffield Hospital Chester Knee Clinic, Autologous Chondrocyte Implantation (ACI), Patient and General Practitioner Information Sheet <<http://www.kneeclinic.info/download/StanmoreACI.pdf>>.

<sup>124</sup> HAS, Transparency Commission, Opinion of 6 October 2010, ChondroCelect, p17.

<sup>125</sup> *Ibid.* p16.

<sup>126</sup> *Ibid.* p16- 17.

registration of the product on the list of drugs that are reimbursed by the national health insurance was thus stopped from this assessment. Consequently, the improvement of medical benefit, the indicator used in France to measure the therapeutic progress, was not even quantified. Thus, in accordance with the French social health insurance code, the registration of ChondroCelect on the list of medicinal products that are authorised for use in regional authorities has been refused and its use cannot be reimbursed by the national health insurance in France.<sup>127</sup> Even though ChondroCelect obtained a renewal of its European marketing authorisation and safety and efficacy post- authorisation studies have been conducted, the Transparency Commission maintained its negative position regarding the registration of ChondroCelect on the list of medicinal products that are authorised for use in regional authorities in an opinion dated from 29 May 2013: after 12 months of following, it considered ChondroCelect has not proved a more significant clinical improvement compare to microfracture or mosaicplasty.<sup>128</sup> Its medical benefit is still considered insufficient,<sup>129</sup> and consequently its improvement of medical benefit has still not been assessed. Thus, it is not eligible to the medico- economic evaluation by the CEESP.

Although I have chosen ChondroCelect as an example because it has been the first cell- based regenerative therapy to obtain a centralised marketing authorisation and because it has been assessed both by NICE and HAS, it should be highlighted that none of the other authorised cell- based regenerative therapies (MACI, Provenge, Holoclar) are currently reimbursed by the English and French health insurance systems. Holoclar has not been assessed for reimbursement yet. Reimbursement for MACI and Provenge has not been recommended by NICE while MACI's authorisation has been suspended for lack of manufacturing site and

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<sup>127</sup> Article R. 163- 33 of the French social health insurance code.

<sup>128</sup> HAS, Transparency Commission, Opinion of 29 May 2013.

<sup>129</sup> The Transparency Commission pointed out: the lack of proved efficacy on clinical criteria; more regular adverse effects (compare to the microfracture technic) which can potentially challenged the interest of an important surgery and have a potential negative impact on the patients' re- education; difficult technic that involves two hospitalisations. Moreover, it exists therapeutic alternatives and for the same reasons than in 2010, a public health interest is not expected for ChondroCelect. *Ibid.* p21.

Provenge's authorisation has been withdrawn at the request of the manufacturing authorisation holder for commercial reasons.

#### IV- CONCLUSION

The reimbursement of the first ATMP was turned down because of inadequate evidence for both the UK and France systems despite their differences and even though the medicinal product was granted a marketing authorisation *via* the centralised procedure. It emphasizes that the efficacy assessed for marketing authorisation is distinct from the 'medical benefit' that is calculated in relative cost terms for reimbursement. The current trend at the EU level is the promotion of early contact with both the EMA for market access and HTA bodies for reimbursement through parallel scientific advices. It has also been emphasized in the EMA pilot project on adaptive pathways launched in March 2014.<sup>130</sup> Thus, researches and discussions through reflexive agencies such as RMEG in the UK as well as early contacts with both regulators and HTA bodies, are necessary to find solutions to fill in the gap between the EU promotion of regenerative medicine access to the market, through the advanced medicinal products legal framework, and the real access of patients to these products once they are authorised on the European market. These regulatory steps are two distinctive "gatekeeping arenas" where special treatments for regenerative medicine through exceptions and exemptions to the general legal frameworks are currently considered.<sup>131</sup> However, the high cost of regenerative therapies will always have to be balanced with the limited national health resources and expenses.<sup>132</sup> In that context, regulations that boost the promotion of public health, such as the current criteria of the impact on public health used by the

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<sup>130</sup> EMA, Pilot project on adaptive licensing, 19 March 2014.

<sup>131</sup> A Faulkner, 'Special treatment? Exceptions and exemptions in the politics of regenerative medicine gatekeeping in the UK in global context', 2015, Working Paper 46, <http://www.kcl.ac.uk/sspp/departments/politiceconomy/research/biopolitics/publications/workingpapers/Working-Papers-41-55.aspx> and Opening the gateways to market and adoption of regenerative medicine? The UK case in context, forthcoming in Regenerative Medicine.

<sup>132</sup> A Mahalatchimy, 'Access to advanced therapy medicinal products in the EU: where do we stand?' (2011) EJHL 18, 305-317.

Transparency Commission in France, or the VbA's discussions in England encourage pharmaceutical research into a different range of conditions. They should be embedded in a discussion that goes beyond cell- based regenerative therapies regarding worldwide equity. Indeed, they counterbalance commercial incentives to invest in expensive therapies to treat chronic illnesses in the Western world while low priority is given to common/acute conditions in the developing world and to the looming global crisis of bacterial resistance to antibiotics. As for ChondroCelect in the UK, it raises again the question of equity and a “two- speeds” access to innovative drugs if they are reimbursed by private insurances only. Contrary to France which is setting- up a general framework for the medico- economic evaluation of health product, the thinking is ongoing in England regarding the adequacy of the current national framework for the efficiency assessment of cell- based regenerative therapies. This is notably due to the national strategy on regenerative medicine and to the establishment of the RMEG. Moreover, a UK Economic and Social Research Council (ESRC) funded project, REGenableMED, aims to examine the dynamics of innovation within the field of regenerative medicine. It is undertaking a detailed analysis of the interplay between business models, measures of clinical utility, patterns of regulatory oversight and clinical workflows within healthcare settings, and specifically considers the reimbursement and the adoption in clinics issues for regenerative medicine.<sup>133</sup> The presence of such project's funding contributes to prove the means that are provided for the promotion of regenerative medicine in the UK and the political interest it raises.

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<sup>133</sup> REGenableMED project <<https://www.york.ac.uk/satsu/current-projects/regenablemed/>>.

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